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ORGANIC NITRATES FOR THE CONTROL OF ANGINA PECTORIS

TREATMENT OF ANGINAL ATTACKS - After decades of use, glyceryl tri-nitrate U.S.P. (nitroglycerin) is still the best drug available for the relief of anginal attacks. Inhalation therapy with amyl or octyl nitrite can be equally effective, but nitroglycerin is cheaper and its dosage more accurately controllable; therefore, the latter, in sublingual tablets, is still the drug of choice.

PREVENTION OF ANGINAL ATTACKS - The choice of drugs for the prevention of anginal attacks is less clear. Conflicting results in apparently well-controlled clinical trials of different drugs reflect the difficulty of appraising their prophylactic effectiveness. Spontaneous and irregular fluctuations in frequency, duration and severity of attacks, and the marked effect of emotional factors complicate the problem of appraisal. Clinical trials, even though carefully controlled, are of little significance unless they are of much longer duration than most of the published studies. As for uncontrolled studies, their unreliability is emphasized by one study in which placebos alone were effective in about 40 per cent of anginal patients (W. Evans and C. Hoyle, Quarterly J. Med., 2:311, 1933).

Many investigators have used electrocardiographic changes as a measure of the effectiveness of drugs in angina. But spontaneous variations in a patient's electrocardiogram, and the impossibility of distinguishing between the effects due to coronary flow and those unrelated to the clinical picture of the anginal syndrome, make the results of such studies questionable. Measurement of nitrate blood levels is also of little value, since it has not been possible to correlate blood levels with the clinical effectiveness of a nitrate drug. Nor do blood levels appear to have significant relationship to the duration of action of these drugs (C. J. Carr, Int'l Rec. Med., 171:121, 1958). Plethysmographic studies of peripheral vessels yield information about the effects of a drug on these vessels but have no bearing on the behavior of the coronary arteries or on effectiveness in the anginal syndrome.

A MORE RELIABLE TEST - The point has been well made that "the only way to determine the clinical usefulness of a drug is to design the test so that the criterion of benefit is the relief of anginal pain..." (L. N. Katz, Ann. N.Y. Acad. Sci., 64:507, 1956). A test in which angina is induced under standardized conditions of exercise has been used by J. E. F. Riseman and his associates (Circulation, 17:22, 1958). This may prove to be a more reliable method of assay.

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NITRATES FOR PROPHYLAXIS - Although the effect of nitroglycerin is usually dissipated within about a half hour, this drug often helps in the prevention of pain if it is taken immediately before activity known to provoke anginal attacks. To help prevent anginal attacks for longer periods (two to four hours), erythrityl tetranitrate N. F. can be used. In a controlled clinical study of nitrites and nitrates by J. E. F. Riseman and his associates (see above) erythrityl tetranitrate was found to be much more effective when dissolved sublingually than when swallowed. Cardilate (Burroughs, Wellcome) is a sublingual erythrityl tetranitrate available in 5- and 15-mg. tablets.

NITROGLYN - Many "long-acting" or "timed-release" preparations are offered for more prolonged protection against anginal attacks, and it is here that there is the greatest gap between the claims and much of the evidence. Nitroglyn (Key), for example, is a sustained-release preparation of nitroglycerin, available in 2.5- and 6.5-mg. oral tablets, which is claimed to be effective over a period of 10 to 12 hours. In the Riseman study cited above it was found that Nitroglyn was of value in about 55 per cent of patients, but most of them required much higher daily dosage than the 5 to 13 mg. recommended by the manufacturer. In a recent controlled trial with a small group of patients, 6.5-mg. Nitroglyn tablets twice daily were no more effective than a placebo (T. R. E. Pilkington and M. J. Purves, Brit. Med. J., 1/2/60, p. 38). The vagaries of gastrointestinal absorption and degradation may be responsible for the ineffectiveness of oral as compared with sublingual preparations of nitroglycerin and other nitrates.

METAMINE - Triethanolamine trinitrate biphosphate (Metamine - Leeming; and other brands) is available in 2-mg. and 10-mg. "sustained" tablets. The recommended dose is one or two 2-mg. tablets four times a day, or one 10-mg. tablet twice a day. This drug was judged to be without effect in doses up to 18 mg. daily in controlled, double-blind trials (S. L. Cole, et al., Circulation, 15:405, 1957; D. G. Friend, et al., Amer. Heart J., 48:775, 1954). In the study by Riseman, et al. cited above, the drug was moderately effective in a minority of patients.

PETN - Pentaerythritol tetranitrate (PETN) is marketed as Peritrate (Warner-Chilcott) in 10-mg. and 20-mg. tablets and as 80-mg. "sustained-action" tablets. Other brands of PETN are also available. There are striking differences of opinion as to its effectiveness in preventing anginal attacks. Favorable results have been reported with doses ranging from 10 to 160 mg. (D. Weitzman, Brit. Med. J., 2:1409, 1953). Two well-controlled studies indicated that the drug was not much more effective than a placebo (S. L. Cole, et al., see above; G. M. Kalmanson, et al., AMA Arch. Int. Med., 95:819, 1955). J. E. F. Riseman, et al. (see above) found the drug to be of moderate value in a small percentage of anginal patients.

ISOSORBIDE DINITRATE - Isosorbide dinitrate (Isordil - Ives, Cameron) is a new nitrate promoted with the claim that it provides "effective control of angina pectoris - reduces number, duration, and severity of anginal attacks." A 4-page advertisement for Isordil in the Jan. 16, 1960 issue of the Journal of the American Medical Association gives seven supporting references. All but one of these are unpublished personal communications and case reports on file with

the manufacturer. The remaining reference is to the Riseman report in the January 1958 issue of Circulation, cited above. This reference follows the sentence in the advertisement, "The only significant side effect [with Isordil] observed to date has been transitory, easily controlled headache, normally considered an expression of effective pharmacodynamic activity." Dr. Riseman's group did not test Isordil; the reference relates only to the last part of the sentence. In the opinion of Medical Letter consultants, the use of Isordil at this point, except experimentally, would be difficult to justify.

In summary, it has not been found that any nitrate will provide consistent or sustained protection against anginal seizures. On the basis of the limited evidence now available, Medical Letter consultants believe that, for prevention of attacks, sublingual erythrityl tetranitrate (Cardilate), taken every two to four hours, is likely to be superior to the "long-acting" nitrates. For immediate relief of the anginal seizure and for protection immediately prior to exertion, sublingual nitroglycerin U.S.P., as pointed out above, is the best drug. (The patient should be cautioned to store and carry nitroglycerin tablets in tightly closed containers, and to keep tablets for no more than a few months.) The optimum dosage of any of the drugs, short- or long-acting, must be determined by trial, and may have to be changed as tolerance is acquired or as the disease progresses.

The following figures show the approximate cost per tablet of the various preparations when they are prescribed in quantities of a hundred:

Nitroglycerin (all sizes) - 1.5¢	Metamine Sustained, 10 mg. - 11¢
Cardilate, 3 mg. - 3¢; 15 mg. - 5.5¢	Peritrate, 10 mg. - 5¢; 20 mg. - 6.5¢
Nitroglyn, 2.5 and 6.5 mg. - 11¢	Peritrate Sustained Action, 80 mg. - 15¢
Metamine, 2 mg. - 7.5¢	Isordil, 10 mg. - 6.5¢

C. V. P.

C. V. P. (U.S. Vitamin), a mixture of a water-soluble citrus bioflavonoid compound and ascorbic acid, is claimed to diminish abnormal capillary permeability and fragility and to reduce bleeding and oozing. The manufacturer suggests its use for "little strokes" and in tonsillectomy and other forms of ear, nose and throat surgery. It is also offered for "fragility and bleeding in hypertension, diabetes, retinopathies, purpura, threatened and habitual abortion, radiation therapy, bleeding gums, epistaxis, duodenal ulcer, gastrointestinal bleeding." It is further claimed to have "significant ameliorative effects... in colds, influenza and certain other respiratory infections."

The effectiveness of one of the ingredients of C. V. P. - vitamin C - in reducing the increased capillary fragility of scurvy and of less overt ascorbic acid deficiency is well established (I. S. Wright and A. Lilienfeld, Arch. Int. Med., 57:241, 1936). But it has never been demonstrated that vitamin C has any effect on the capillaries in the absence of a deficiency of the vitamin.

THE FLAVONOIDS - The other ingredient of C. V. P. - a complex of water-soluble flavonoids - occurs naturally in citrus peel and pulp, and it is claimed

by the manufacturer to be more active than such insoluble flavonoids as rutin and hesperidin. Evidence has been offered to show that the flavonoids in C. V. P. are biologically active in experimental animals when high concentrations are injected directly into a capillary bed (V. Menkin, Am. J. Physiol., 196:1205, 1959).

Observations of lessened capillary fragility following the use of bioflavonoids or of C. V. P. cannot be given much weight, since it is well-known that the techniques for measuring capillary fragility are crude procedures "fraught with difficulty." (Goodman & Gilman, Pharmacological Basis of Therapeutics, p. 1726). In one recent study (C. S. Mumma, et al., Eye, Ear, Nose and Throat Monthly, 38: 934, 1959), when C. V. P. was given prior to and following tonsillectomy, blood loss correlated not with administration of C. V. P., but with the experience and skill of the surgeons. C. V. P. is claimed to be of value in hemorrhagic diathesis. A study of the drug's effectiveness in one important diathesis - hemophilia - was recently reported by Dr. A. J. Quick. On the basis of this study, the Bulletin of the Midwest Chapter of the National Hemophilia Foundation, Nov. 1959, states: "The [Medical Advisory] Council made a final report on the survey of two years' use of C. V. P. by a selected group of hemophiliacs who alternated each year with placebo. The council members present agreed that C. V. P. does not appear to have any favorable therapeutic results in hemophilia."

In fact, despite many favorable studies, it has not been demonstrated that the clinical effectiveness of C. V. P. is superior to that of ascorbic acid alone, and the latter is effective only where there is a vitamin C deficiency. In the absence of reliable studies showing its value, C. V. P. cannot be recommended for diabetic retinopathies, "little strokes," or any other condition.

PINWORMS

Pinworm infestation appears to be one of the many conditions in which reassurance may be as important as medication. Commenting on the Medical Letter review of anthelmintic drugs (2:4, Jan. 8, 1960), Dr. J. R. Paul, Jr., Professor of Pediatrics at the Medical College of South Carolina, agrees that the piperazine drugs (such as Antepar) are effective against enterobiasis, but he doubts the value of measures used to prevent reinfestation. "I have seen a good many families who have spent literally years trying to rid themselves of enterobiasis, and becoming rather severely emotionally disturbed about these completely harmless creatures," he writes. "I do not believe that it is necessary to do pinworm swabs on children who do not have symptoms, as I am convinced that pinworms are occasional if not long-term virtually saprophytic inhabitants of the rectum of up to 100 per cent of school children. . . . I think there is much less evidence that pinworms have anything to do with producing disease than there is against the common house fly." The editors of The Medical Letter agree that in the absence of such symptoms as itching and irritation, pinworm infestations can safely be ignored. Although the value of the extreme sanitary measures sometimes recommended for the prevention of reinfestation is questionable, when treatment is undertaken, it is probably desirable that the hands be washed before meals, and cotton undergarments changed twice a day; also that bedroom and bathroom floors be washed at the end of the treatment course.